

REMARKS

Claims 1-20 are pending and are presently under examination. The specification has been amended on page 1 to update the priority claim. Claim 1 has been amended. Support for the amendment to claim 1 can be found, for example, at page 7, lines 2-13, and the amendment has been made for clarity and does not narrow the scope of the claim. Accordingly, these amendments do not raise an issue of new matter, and entry thereof is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1, 2 and 4-20 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods.

Applicants submit that one skilled in the art would have been able to make and use the invention as claimed. The claimed methods are directed to diagnosing or predicting susceptibility to an autoimmune disease associated with a 2-2-4 haplotype at the Notch4, HSP70-HOM, D6S273 loci by determining in the individual the presence or absence of the 2-2-4 haplotype, or a disease associated haplotype or allele associated with the 2-2-4 haplotype. It is respectfully submitted that knowledge of the function of the genes making up the 2-2-4 haplotype would not have been required to diagnose or predict susceptibility to an autoimmune disease as claimed.

A strong association between the 2-2-4 haplotype and autoimmune disease was the basis for the claimed methods. As disclosed in the specification at page 7, lines 3-11, and as shown in Figure 3, a 2-2-4 Notch 4, HSP70-HOM and D6S273 haplotype was transmitted to affected individuals 16 times and not transmitted 2 times, indicating a strong association between this MHC class III 2-2-4 haplotype and autoimmune diseases such as Crohn's disease (see also Example IV). Knowledge of the function of any of the genes of the 2-2-4 haplotype is independent of the observed correlation between this haplotype and autoimmune disease and would not have been required to diagnose or predict susceptibility as claimed. As evidence that allelic association can be useful even when there is no direct biological action of the

polymorphism, Applicants submit herewith as Exhibit A, Pericak-Vance, "Linkage Disequilibrium and Allelic Association" in Haines and Pericak-Vance, Approaches to Gene Mapping in Complex Human Diseases (1998) Wiley-Liss, New York. As stated at page 323, "Allelic association can be explained either by direct biological action of the polymorphism (e.g. the APOE-4 allele in Alzheimer disease), or by linkage disequilibrium with a nearby susceptibility gene" (emphasis added). Thus, an allele or haplotype associated with a disease and useful in diagnosing or predicting may have a function relevant to the disease being diagnosed, or, alternatively, may be in linkage disequilibrium with the actual disease-causing or susceptibility gene. In view of the above remarks and the evidence submitted herewith, Applicants maintain that it would not have been necessary to know the function of one or all of the Notch4, HSP70-HOM and D6S273 genes.

Moreover, amended claim 1 is directed to a method of diagnosing or predicting susceptibility to an autoimmune disease "associated with a 2-2-4 haplotype at the Notch4, HSP70-HOM and D6S273 loci" and, therefore, does not encompass methods of diagnosing autoimmune diseases that are not associated with the 2-2-4 haplotype. Applicants respectfully submit that only routine methods, such as those taught in the specification and discussed above, would have been required to confirm association of the 2-2-4 haplotype with an autoimmune disease such as rheumatoid arthritis, Type I diabetes or ulcerative colitis. Again, the claimed methods do not encompass diagnosis of diseases that are not associated with the recited 2-2-4 haplotype; any "inactive" embodiments are not within the scope of the claims.

The Office Action asserts that no working examples are provided. Applicants respectfully point out that a working example is not required for enablement, in particular if one skilled in the art is able to practice the invention without undue experimentation (see MPEP § 2164.02). With regard to a disease-associated haplotype or allele associated with a 2-2-4 haplotype, Applicants respectfully submit that the use of a surrogate allele or haplotype, which is associated with a genetic marker such as the 2-2-4 haplotype having a known association with a disease, is well known in the art. For example, the specification teaches that a disease-associated haplotype or disease-associated allele associated with the 2-2-4 haplotype means that the disease-associated haplotype or disease-associated allele and the 2-2-4 haplotype are inherited together

more often than would be expected according to traditional Mendelian genetics (page 23, lines 19-25). The specification further teaches that the presence of a disease-associated haplotype or allele associated with the 2-2-4 haplotype can be used as a surrogate for the 2-2-4 haplotype to diagnose or predict susceptibility to an autoimmune disease such as Crohn's disease (page 23, lines 25-32). Moreover, the specification teaches that one or more of the Notch4 allele 2, HSP70-HOM allele 2 or D6S273 allele 4 can be substituted with an alternative genetic marker to produce another diagnostic haplotype and teaches exemplary genetic markers that can be a disease-associated allele or that can be combined with, or substituted within, the 2-2-4 haplotype to produce a disease-associated haplotype (page 24, line 1, to page 28, line 7, and Table 1). Accordingly, Applicants respectfully submit that methods of determining the association of a surrogate allele or haplotype with a marker such as the 2-2-4 haplotype were well known to those skilled in the art.

With regard to the alleged unpredictability and amount of experimentation, Applicants point out that claim 1, as amended, is directed to a method of diagnosing or predicting susceptibility to an autoimmune disease associated with a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci in an individual by determining the presence or absence in the individual of the 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci, wherein the presence of the 2-2-4 haplotype is diagnostic of or predictive of susceptibility to the autoimmune disease. Accordingly and as discussed above, the claims are directed to those autoimmune diseases associated with a 2-2-4 haplotype. Therefore, the issues raised in the Office Action regarding the alleged unpredictability of the association of a particular haplotype with a particular autoimmune disease are not relevant since the claims are directed to diagnosing or predicting susceptibility to an autoimmune associated with a 2-2-4 haplotype. With regard to the amount of experimentation required to practice the claimed invention, Applicants respectfully submit that any experimentation required to practice the claimed invention involves routine methods well known in the art or taught in the specification (see Examples).

In view of the guidance provided in the specification, undue experimentation would not have been required to use the recited 2-2-4 haplotype to diagnose or predict susceptibility to a variety of autoimmune diseases as claimed. Guidance is provided in the specification, which

teaches that the methods of the invention are useful for diagnosing or predicting susceptibility to an autoimmune disease, which is a term well known in the art to mean a disease resulting from an immune response against a self tissue or tissue component (see specification at page 11, lines 15-22). Exemplary autoimmune diseases include organ-specific and non-organ specific autoimmune diseases such as Crohn's disease, ulcerative colitis, Type I diabetes mellitus, and rheumatoid disease as set forth in the specification (page 11, line 22, to page 12, line 7). Thus, the specification provides guidance for the skilled person regarding practicing the invention for diagnosis of a variety of autoimmune diseases, including but not limited to Crohn's disease.

In addition, a variety of autoimmune diseases were known to share common features, further substantiating that the 2-2-4 haplotype would have been used to diagnose or predict susceptibility to Crohn's disease or another autoimmune disease, as claimed. As support for the assertion that there are common genetic factors that contribute to multiple distinct autoimmune diseases, Applicants submit herewith Becker et al., Proc. Natl. Acad. Sci. USA 95:9979-9984 (1998), attached as Exhibit B. Becker et al. report that autoimmune diseases share common features and are associated with markers falling into common genetic clusters. Specifically, Becker et al. conclude that clinically distinct autoimmune diseases can be controlled by a common set of susceptibility genes because the majority of positive linkages for human autoimmune diseases map non-randomly to distinct clusters (see page 9979, abstract). Becker et al. further report a number of common elements among clinically distinct autoimmune diseases including population frequencies, geographical distributions, clinical features, therapeutic strategies and similar gender ratios (see page 9979, column 2, lines 17-26), stating that

[t]he occurrence of common features of autoimmune diseases and the coassociation of multiple autoimmune diseases in the same individual or family supports the notion that there may be common genetic factors that predispose to autoimmunity

(page 9979, column 2, lines 26-30). In sum, Becker et al. indicate that autoimmune diseases can share common features and that the same predisposing mutation can contribute to multiple distinct autoimmune diseases. Thus, Becker et al. corroborate that the 2-2-4 haplotype can be used to diagnose or predict susceptibility to distinct autoimmune diseases as claimed.

As additional evidence that the 2-2-4 haplotype can be associated with a variety of autoimmune diseases in addition to Crohn's disease, Applicants provide evidence that the MHC region in which the 2-2-4 haplotype resides can be associated with a number of different autoimmune diseases (page 6, lines 13-17, and page 11, lines 1-3). In this regard, see Becker et al. (Exhibit B), which reports that the MHC is one of the central genetic factors recognized in autoimmune diseases (page 9979, column 1, second paragraph of the introduction). Similarly, Vaidya et al., Hum. Mol. Gen. 8:1195-1199 (1999), attached as Exhibit C, reports that the MHC locus is associated with the autoimmune disease Graves' disease. Specifically, Vaidya et al. indicate that the MHC locus confers 17-20% of the genetic susceptibility to Graves' disease and, when taken together with the CTLA-4 locus, the two loci confer approximately 50% of the inherited susceptibility to Graves' disease in the population studied (page 1198, column 1, lines 2-6). Applicants further point out that the D6S273 locus is associated with Type I diabetes and rheumatoid arthritis (see specification at page 10, lines 24-33), further supporting that the 2-2-4 haplotype can be associated with autoimmune diseases such as Type I diabetes and rheumatoid arthritis in addition to Crohn's disease. In sum, the specification and additional publications attached hereto confirm that markers within the MHC region can be associated with a variety of autoimmune diseases and corroborate that one skilled in the art would have been able to practice the full scope of the invention with a variety of autoimmune diseases as claimed.

In light of the above, Applicants maintain that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 13-20 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description is respectfully traversed. Applicants respectfully submit that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed.

Claims 13 and 17 are directed to methods of diagnosing or predicting susceptibility to Crohn's disease in an individual by determining the presence or absence in the individual of a disease-associated haplotype or disease-associated allele associated with a 2-2-4 haplotype at the

Notch 4, HSP70-HOM and D6S273 loci, wherein the presence of the disease-associated haplotype or allele is diagnostic of or predictive of susceptibility to Crohn's disease. As discussed above, Applicants respectfully submit that the use of a surrogate allele or haplotype, which is associated with a genetic marker such as the 2-2-4 haplotype having a known association with a disease such as Crohn's disease, is well known in the art. For example, the specification teaches that a disease-associated haplotype or disease-associated allele associated with the 2-2-4 haplotype means that the disease-associated haplotype or disease-associated allele and the 2-2-4 haplotype are inherited together more often than would be expected according to traditional Mendelian genetics (page 23, lines 19-25). The specification further teaches that the presence of a disease-associated haplotype or allele associated with the 2-2-4 haplotype can be used as a surrogate for the 2-2-4 haplotype to diagnose or predict susceptibility to an autoimmune disease such as Crohn's disease (page 23, lines 25-32). Moreover, the specification teaches that one or more of the Notch4 allele 2, HSP70-HOM allele 2 or D6S273 allele 4 can be substituted with an alternative genetic marker to produce another diagnostic haplotype and teaches exemplary genetic markers that can be a disease-associated allele or that can be combined with, or substituted within, the 2-2-4 haplotype to produce a disease-associated haplotype (page 24, line 1, to page 28, line 7, and Table 1). Accordingly, Applicants respectfully submit that methods of determining the association of a surrogate allele or haplotype with a marker such as the 2-2-4 haplotype were well known to those skilled in the art.

Applicants maintain that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Double Patenting Rejection

The rejection of claims 1-3 and 5-12 under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over claims 1-8 of U.S. Patent No. 6,376,176 is respectfully traversed. Applicants respectfully request that this rejection be held in abeyance until there is an indication of allowable subject matter.

In re Application of:
TAYLOR, Kent D., et al.
Application No.: 10/075,425
Filed: February 12, 2002

PATENT
Attorney Docket No.: 066783-0042

CONCLUSION

The Examiner is respectfully requested to consider the above remarks. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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